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REVIEW

Critiquing Clinical Research of New Technologies for Diabetic Foot Wound Management

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Healing the diabetic foot ulcer has been a challenge. Over the past 20 years, researchers have gained significant knowledge about the biochemical mechanisms that underlie the process of wound repair. A literature review of the latest advanced technologies, devices, and therapies is provided. In addition, clinical decision-making insights for clinicians to evaluate research and to assist in choosing the correct modality for each of their diabetic foot ulcer patients are discussed. (The Journal of Foot & Ankle Surgery 41(4):251-259, 2002)

Key words: diabetic foot, growth factors, tissue replacement, ulceration (ulcers), wound healing

The following facts and figures illustrate the magnitude of the challenge faced by providers of diabetic wound care:

- Of the 16,000,000 people with diabetes in the United States, approximately 2,400,000 (15%) will develop an ulcer in their lifetime (1-3).
- Of those patients hospitalized with diabetes as part of their admitting diagnosis, one-fifth had ulcers (4).
- Diabetes increases a patient's risk of amputation 15-40 times higher than that in people without diabetes (5).
- From 1989 to 1992, an average of 52,000 amputations were performed each year on diabetic patients in the United States (6). In 1996, that number increased to 86,000, an increase of nearly 2.5-fold (5).
- The average cost of healing a diabetic ulcer is in the range of $10,000-$60,000 depending on the severity of the wound (7).
- The total direct cost of amputation is $40,000 for minor amputations and $60,000 for major amputations (8).
- The morbidity and mortality of diabetic foot ulcers is substantial (9): 39-68% of those who suffer an amputation will die within 5 years (10, 11).

With these facts in mind, it becomes clear that there is a tremendous need for treatments that will reduce the human and economic loss associated with diabetic foot ulcers and lower extremity ulcerations.

Centuries ago, it was believed that an open wound was an indication that something inside the body needed to escape. It is still commonly believed that it is beneficial to leave a wound open to the air or to cover it with a dry dressing for normal healing to occur. It has now been clearly shown that a moist wound environment is preferable to dry healing (12-14). Literally hundreds of different topical agents have been applied prior to the development of modern technologies. Honey, sugar, bread poultices, and mud are examples of some ancient wound treatments. Herbal remedies have been utilized in Asia for thousands of years. Saline, antiseptic solutions, and topical antibiotics are now commonly used. Some of these topical agents enhance wound healing, while others are cytotoxic to the healing process (15-22).

In the last two decades, however, wound healing has moved from a passive through an interactive phase of wound management and into a "bioactive" phase made possible by new technology. The interactive phase was

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TABLE 1 Basic principles of chronic wound management

• Perform a detailed assessment
• Ensure adequate blood supply
• Prevent further trauma
• Prevent or resolve infection
• Utilize a multidisciplinary team
• Prevent recurrence
• Optimize the wound environment

notable for the use of a variety of moisture-retentive and absorbent dressings to maintain a hospitable wound environment. A great deal is now known about the regulation, deposition, and remodeling of extracellular matrix, which is responsible for maintaining the physical integrity of the wound site and for guiding the movement of cells within that compartment (23). This new bioactive approach elicits host cellular and biochemical responses that accelerate the rate and possibly the quality of healing.

Basic Principles of Quality Wound Care

In the evaluation of any paper describing new therapies for treating diabetic foot ulcers, it is important to recognize that comprehensive wound care is the cornerstone of any treatment protocol (Table 1). If these key factors are not adequately managed, the actual substance makes little difference in the overall process. Even advanced, bioactive therapies cannot overcome inadequate wound care. The presence of a comprehensive protocol is one of the primary considerations when evaluating studies on this topic. Detailed descriptions of these principles of wound care are described in several documents, including American Diabetes Association: *Clinical Guidelines for Diabetic Foot Care* (24), and American College of Foot and Ankle Surgeons and the American College of Foot and Ankle Orthopedics and Medicine: *Diabetic Foot Disorders: A Clinical Practice Guideline, 2000* (25).

Clinician's Judgment as to Product Choice

Once these basic principles of wound care are met, the clinician can then evaluate which of the passive, interactive, or bioactive wound treatment interventions would best assist in addressing the deficiencies of repair and healing the wound. Evidenced-based medicine is the hallmark of decision making today in the health care field. Widely accepted, traditional treatment interventions may not be the most efficacious at the present time. Physicians and health professionals need to be open to these new practices so patients can benefit from these newer modalities.

When evaluating a new product, the clinician needs to evaluate the published clinical research. Aside from the assessment of the literature review, methodology, results, conclusions, and discussion, the questions listed in Table 2 should be asked. In addition, many of the Blue Cross agencies across the United States use the following Medical Technology Assessment Guidelines to determine whether a specific technology improves health outcomes (26):

1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives; and
5. The improvement must be attainable outside the investigational settings.

In June 2000, the Food and Drug Administration (FDA) developed a draft document entitled *Guidance for Industry: Chronic Cutaneous Ulcer and Burn Wounds — Developing Products for Treatment* (27). Some definitions in this document set a new standard for clinical research and include:

- A chronic cutaneous ulcer is defined as a wound that has failed to proceed through an orderly and timely series of events to produce a durable structural, functional, and cosmetic closure.
- Complete closure is defined as skin closure without drainage or dressing requirements. This is probably the most clinically meaningful definition related to improved wound healing.
- Efficacy or success would be defined as a statistically significantly greater proportion of those patients assigned active product achieving closure compared to the control arm.
- While complete closure is the preferable end point, other parameters may be considered: accelerated wound closure, facilitation of surgical closure, or improved quality of healing.

Dressings

Despite the fact that more than 1,000 products exist for use in patients with chronic ulcers, the perfect dressing or topical agent does not yet exist. How does the clinician choose between the hundreds of alternatives? By becoming familiar with the characteristics of the different types of dressings, one can select the appropriate wound care regimen for any wound (28–30). Correlation of the wound characteristics with the properties of a specific

TABLE 2 Critiquing published clinical research

Questions to Ask When Comparing Clinical Research Studies	Yes/No	Preferred Response
Were the types of wounds studied the same?		Yes
Were the inclusion/exclusion criteria the same for each study?		Yes
Were the treatment interventions similar?		Yes
Were the intervening variables similarly controlled (i.e., the amount of off-loading)?		Yes
Was the study a randomized controlled trial, which is the gold standard for clinical research?		Yes
Was the control arm the same in terms of standard care?		Yes
Was the clinical protocol similar?		Yes
Were the patients in each arm treated with comprehensive wound management?		Yes
Was the length of treatment the same in each study or study arm?		Yes
Was there a statistically significant difference between the control arm and the treatment arm?		Yes
Between studies, was there a larger percentage of difference between the control arm and the treatment arm?		Yes
Was the end point the same in each study?		Yes
Did each study use the same definition for the end point (i.e., complete closure, rate of healing, or percentage of wounds achieving a certain percentage of area reduction)?		Yes
Was the efficacy documented in each study?		Yes
Was the safety documented in each study?		Yes
Was the cost-effectiveness documented?		Yes
Was pain management evaluated?		Yes
Was quality of life for the patient evaluated and was the same validated tool applied between studies?		Yes
Were the adverse events documented?		Yes
Between studies, were the data evaluated uniformly (i.e., both intent-to-treat versus evaluable subjects)?		Yes
If the study is a meta analysis, have the strict rules been followed regarding pooling data?		Yes

dressing will help optimize care. The following is a description of some of the most popular dressing categories (31):

- *Gauze* — While gauze has been used for wet-to-dry dressings, wet-to-moist dressings have replaced this regimen. Prepackaged dressings with gauze or pillow-type pads impregnated with saline, Ringer's lactate, or hydrogels are now available which decrease the frequency of dressing changes. The increased cost of the material and packaging is offset by the reduction in staff time to perform multiple dressing changes.
- *Antimicrobials* — These include products such as silver dressings that provide topical antimicrobials that function to control infection.
- *Transparent films* — These products are not absorbent and are suitable for shallow wounds such as donor sites, blisters, and abrasions.
- *Hydrocolloids* — These materials have broader indications for a variety of wounds, including those that are deeper and more exudative.
- *Wound fillers* — These may be left in place for more than 1 day and absorb a significant amount of drainage.
- *Hydrogels* — Whether in a preformed sheet or an amorphous gel, they are composed primarily of water and therefore are not as absorbent as other dressings. Some hydrogels contain additives such as aloe derivatives and hypertonic saline.
- *Foams* — These products are available in several thicknesses and densities, and are capable of absorbing significant amounts of drainage and maintaining a moist wound contact layer.
- *Alginates* — Alginates are available in sheets or packing strips and are woven dressings made of refined seaweed. They can absorb many times their weight in wound exudate and are therefore helpful in highly exudative wounds, such as venous insufficiency ulcers.
- *Collagens* — Both avian and bovine varieties have been used in wound management. Available in sheets, granules, and pastes, collagen is recognized as a fundamental building block in the wound-healing process. However, a paucity of evidence exists to support their use in chronic wounds and there are concerns regarding allergic reactions or disease transfer issues.
- *Composite dressings* — Composite dressings are combination dressings that provide both absorptive and retention characteristics.

- *Temporary wound dressing* — A porcine-derived, small intestinal submucosa is available to treat partial-thickness wounds.

Hydrogels, foams, hydrocolloids, and films are moisture-retentive dressings. Gauze, alginates, collagen, and a number of composite dressings are moisture-absorbing dressings. A moist wound environment can be achieved with either type of dressing.

Devices

A number of devices for treating the chronic wound have been introduced. The research regarding these devices should also be critiqued using the previously mentioned guidelines.

Hyperbaric Oxygen Therapy

While there is a growing body of literature supporting the adjunctive use of hyperbaric oxygen in diabetic ulcers, there is still caution due to the lack of randomized, placebo-controlled trials (32–39). Exposure to 100% oxygen at 2 atm of pressure enhances neovascularization, increases the production of collagen, and enhances the ability of neutrophils to kill microbes. It also increases the synthesis of platelet-derived growth factor (PDGF). If there is no significant enhancement in the transcutaneous oxygen tension with hyperbaric oxygen treatment, then there is little indication for its use.

Electrical Stimulation Therapy

Electricity has been studied for centuries as an aid to healing. Abundant literature demonstrates the benefit of electrical current in the healing of bones. It is therefore not surprising that electrical stimulation has been investigated for healing soft-tissue lesions as well (40–53). Electrical current can improve blood flow, reduce edema, and inhibit bacterial growth. Electrical stimulation also increases protein synthesis and growth factor expression in human fibroblasts (54–55).

Cell Proliferation Induction (CPI®)

This therapy (Provant™ Wound Closure System)[2] is based on the mitogenic properties of a specific, localized radiofrequency signal, which promotes the release of endogenous, growth-promoting factors in vitro. These multiple endogenous growth factors selectively target quiescent or compromised fibroblasts and epithelial cells within a wound. Clinical results show that CPI therapy accelerates wound repair to full closure and is effective for treatment of wounds of various etiologies (56–60).

Ultrasound Therapy

Ultrasound is a useful diagnostic tool and is frequently used to treat inflammation. It reduces edema, impacts local circulation, and has an effect on collagen synthesis (61–63). A meta-analysis of several controlled studies on chronic wounds demonstrated a statistically significant mean difference in healing compared to control when ultrasound was used (16.9% at 4 weeks and 14.5% at 8 weeks) (64). Some case reports have recently been presented of the use of noncontact ultrasound through a media of atomized vapor mist (MUST™, Mist Ultra-Sound Technology)[3] on the wound bed of chronic wounds. Initial reports show promise (65–69).

Negative Pressure Wound Therapy

This therapy utilizes vacuum-assisted closure (V.A.C.®).[4] This subatmospheric pressure technique reduces chronic edema, leading to increased localized blood flow. The applied forces result in the enhanced formation of granulation tissue. This technique is cost-effective and Medicare reimbursement is available for this product (70–72).

Radiant Heat Warming Therapy

The hypothesis behind normothermia is that all cellular functions and enzymatic and biochemical reactions are optimized at normal body temperature. A semi-occlusive, noncontact, heated dressing (Warm-Up Active Wound Therapy)[5] was found to provide a statistically significant reduction in mean surface area of pressure ulcers (60.73% for the treatment arm versus 19.24% for the control arm). Published studies have described efficacy in pressure ulcers, venous ulcers, and surgical wounds (73–78).

Bioactive Therapies

Three of the more intriguing wound care modalities are keratinocyte cultures, growth factors (both platelet releasate and recombinant), and tissue replacements (sometimes called "living skin equivalents" or "skin substitutes").

[2] Regenesis Biomedical, Scottsdale, Az.

[3] Celleration, Eden Prairie, MN.
[4] KCI USA, San Antonio, TX.
[5] Augustine Medical, Inc, Eden Prairie, MN.

Keratinocyte Cultures

Through the technique of autogenic keratinocyte cultures, a small graft of skin (typically from the forearm) of approximately 1 cm^2 can be expanded into a larger sheet 100–100,000 times its original size. Typically, it takes about 3 weeks to grow a sufficient amount of material. The resultant graft is quite fragile, but it is possible for the layer of living keratinocytes to be applied with a synthetic backing such as silicone. The best indication for keratinocyte cultures is cases of major tissue loss (e.g., burn patients) (79–81). A temporary covering such as cadaver or porcine skin is required while waiting for the keratinocyte graft. This technology has also been explored in venous insufficiency ulcers (82). One of the disadvantages of this approach is the length of time. It may be difficult to justify the expense of keratinocyte grafts when dealing with small wounds.

Growth Factors

There has been considerable interest in the use of topically applied growth factors since pioneering work in the early 1980s. The critical role played by growth factors in the healing process is well established. Growth factors are both mitogens and chemotactic agents (83–85). Two growth factor solutions have been available: Procuren® solution,[6] a platelet releasate, and Regranex®[7], a recombinant PDGF.

Procuren, an autologous platelet releasate containing a mixture of growth factors, has been available only through a Wound Care Center system managed by Curative Health Systems, Hauppauge, NY. Blood is drawn from the patient, the platelets are isolated, then induced to release growth factors from the alpha granules. The growth factors are then placed into a buffered solution and frozen in individual doses. The doses are thawed as needed, applied to gauze, and placed daily into the wound. A number of analytic studies and smaller clinical trials have been undertaken, and generally have been supportive of the use of platelet releasate (86–90). A major retrospective cohort study ($n = 26,599$ patients) found that the platelet releasate was more effective than standard care and the effect was greatest in those patients with the most severe wounds (i.e., large wounds that affect deeper anatomical structures) (91). In 2001, Procuren was removed from the U.S. market for commercial reasons.

The FDA has approved Regranex gel (becaplermin, recombinant human PDGF-BB isoform) for use in diabetic foot ulcers. After the wound has been cleared of infection and after all necrotic tissue has been removed, a thin layer of gel is applied to the base of the wound daily. In a multicenter, double-blind, placebo-controlled trial of 118 patients, the incidence of complete ulcer closure for Regranex gel 0.003% ($n = 61$) was 48% versus 25% for placebo gel ($n = 57$). A second multicenter, double-blind, placebo-controlled trial of 382 patients showed the incidence of complete ulcer closure for Regranex gel 0.01% ($n = 123$) was 50% versus 36% for placebo gel ($n = 127$). A third multicenter controlled trial of 172 patients assessed the safety of vehicle gel placebo ($n = 70$) compared to good ulcer care alone ($n = 68$). The study included a small ($n = 34$) Regranex gel 0.01% arm. Incidences of complete ulcer closure were 44% for Regranex gel, 36% for placebo gel, and 22% for good ulcer care alone. In another multicenter, evaluator-blinded, controlled trial of 250 patients, the incidences of complete ulcer closure in the Regranex gel 0.01% arm ($n = 128$) (36%) and good ulcer care alone ($n = 122$) (32%) were not statistically different. In summation, the overall difference between control healing and Regranex indicates a 43% improvement (92, 93).

Tissue Replacements

An understanding of normal skin structure and function as well as the cellular function and its interaction with keratinocyte migration has led to the development of various biologic wound treatments. While the epidermal layer can rapidly reform over a wound, the underlying dermis is more difficult to replace. In the past, porcine skin, amnion, cadaver allografts, autologous grafts, and tissue-engineered grafts have been used as biologic coverings.

Advancements in tissue engineering technology have made it possible to create in the laboratory living allogeneic replacements for several different types of tissue such as skin, cartilage, and cardiac valves (94). Two of the tissue replacements that are most applicable to chronic wound care in the lower extremities are Apligraf®[8] and Dermagraft®.[9] The source of the allogeneic fibroblasts is neonatal tissue. Because neonatal tissue does not promote a significant degree of antigenicity, rejection of tissue replacement grafts is not anticipated (95–97).

Apligraf (Graftskin) is a bi-layer tissue replacement that includes an epidermal equivalent layer containing keratinocytes, and a dermal equivalent layer composed primarily of bovine collagen and neonatal fibroblasts (98, 99). The product is packaged ready for application and is shipped to order for specific patients. It must be used within 5 days of shipment. After rinsing

[6] Cytomedix, Deerfield, IL.
[7] Ortho-McNeil, Raritan, NJ.
[8] Novartis, East Hanover, NJ.
[9] Smith & Nephew, Largo, FL.

and trimming to the appropriate size, Apligraf may be secured with stitches or staples to the wound bed. Up to five applications are typically employed. A venous leg ulcer study by Sabolinski indicated that Apligraf can increase the rate of healing and shorten the time to complete healing over compression therapy alone (57 days versus 181 days, respectively) (100). A diabetic foot ulcer study of 208 patients found that 56% of the Graftskin-treated patients achieved complete closure at 12 weeks versus 38% of the control group (101). The difference between control healing and Apligraf healing showed a 49% improvement. During this study, the foot ulcers were completely off-loaded with crutches, wheelchairs, and a customized tridensity sandal. This is more rigorous off-loading than tends to occur in clinical practice.

Dermagraft is a human fibroblast-derived dermal replacement, developed as an implant for the treatment of full-thickness diabetic foot ulcers. It is manufactured through the three-dimensional cultivation of human diploid fibroblast cells on a bioabsorbable polyglactin scaffold. The product is then cryopreserved for later use. The fibroblasts secrete a mixture of growth factors and matrix proteins to create a living dermal structure which remains metabolically active after being implanted into the patient's wound bed (102, 103). Aside from prolonging the shelf life for up to 5 months, the cryopreservation process also stresses the cells, which on thawing have been shown to produce a burst of growth factor production (VEGF) that immediately can provide a healing stimulus to the wound (104). The human fibroblast cell strains used to produce Dermagraft are established from the circumcised foreskins of newborns and cultured by standard methods. After cell expansion, a single donor foreskin provides sufficient cell seed to produce 250,000 square feet of finished tissue. Research has demonstrated that the fibroblasts in the graft produce the key elements of wound healing, including growth factors, glycosaminoglycans, and matrix proteins (105).

An initial pilot study of 50 diabetic foot ulcer patients showed that 50% of the Dermagraft-treated ulcers healed in 8 weeks compared with 8% of the control group. After a mean of 14 months, there were no recurrences in the Dermagraft-healed ulcers (106). A pivotal multicenter, prospective, randomized, controlled trial of 281 diabetic patients with neuropathic, full-thickness plantar foot ulcers was conducted. A total of 50.8% of the Dermagraft-treated patients experienced wound closure within 12 weeks, while only 31.7% of controls did. This was a 60% improvement (107). A follow-up trial of 50 patients with diabetic foot ulcers was conducted. The pooled data from these two studies demonstrated that 51% of the Dermagraft-treated wounds healed versus 31.7% of the control group (108).

Discussion

The abundant research in the field of wound healing has given the clinician exciting new tools, unprecedented opportunities, and higher standards for which to aim. However, none of the new technologies will be effective unless coupled with appropriate overall wound management. Adherence to the basic principles of wound management is the foundation for success in the treatment of chronic wounds.

Despite a growing understanding of the process of wound healing and several new advances in technology, many unanswered questions remain. In the past, valid comparison between modalities or even between different studies of the same modalities was difficult because common definitions did not yet exist. For example, there is no universally accepted definition of complete healing or complete epithelialization. The new FDA guidelines will make it easier to compare clinical trial protocols and results. Wound care studies will become more similar, such as testing the same wound etiology, using the same off-loading techniques, noninvasive vascular testing, neuropathy testing, measurement techniques, and evaluation of wound characteristics. This has been lacking in the past. Consistency through standardization and common definitions will aid the scientific community in the assessment of new approaches to wound management.

In addition to the issues of standardization between studies of new technologies, other considerations such as ease of use and accessibility must be evaluated. What is the product's shelf life? Is it necessary to purchase a freezer? How many treatments or treatment sessions are required? Is the product only available in selected centers?

It is important for the clinician to be educated in the science of wound healing and understanding the deficiencies of repair that cause the levels of wound chronicity seen in clinical practice. It is also important to recognize, in the newer advanced therapies, that single growth factor gels or cells grown on different scaffolds and subsequently delivered fresh or cryopreserved may have different mechanisms of action in targeting the underlying problems of repair; thus they will not always provide the same benefits. Scientific and clinical evidence sought by the physician for review should help in making the appropriate choice.

Finally, one of the most significant considerations in the evaluation of the newer technologies for wound management is cost. The ultimate cost can only be determined through health economics research focused on outcomes (109, 110). In this era of managed care, it is imperative that patients, physicians, insurers, and industry collaborate to define what constitutes truly cost-effective care.

Summary

It is important for a clinician to become skilled in critiquing the clinical research literature. By doing this, he or she can accurately determine the optimal products to use when treating diabetic foot ulcer patients. The questions and definitions described in this article can assist the clinician in this endeavor.

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